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# The alternate-day fasting diet is a more effective approach than a calorie restriction diet on weight loss and hs-CRP levels

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**Abstract:** Background and Objective: The aim of present study was to compare, and determine, the effects of a modified alternate-day fasting diet vs. calorie restriction on inflammatory indices and coagulation factors. Methods: This was a randomized clinical trial consisting of 80 metabolic syndrome patients, who were enrolled and randomly dichotomized into a modified alternate-day fasting diet or calorie restriction group for 4 months. We measured weight, body mass index (BMI), waist circumference (WC), waist-hip-ratio (WHR) and fat mass as primary outcomes and assessed high sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF- $\alpha$ ) and coagulation factors levels as secondary outcomes before and after intervention. Results: Compared to the calorie restriction diet, following a modified alternate-day fasting diet led to a greater reduction in body weight (kg) ( $-6.43 \pm 4.34$  vs  $-4.11 \pm 4.27$ ;  $P = 0.02$ ), BMI ( $\text{kg/m}^2$ ) ( $-3.19 \pm 2.90$  vs  $-1.43 \pm 2.72$ ;  $P = 0.01$ ), fat mass (kg) ( $-4.88 \pm 2.09$  vs  $-3.72 \pm 2.43$ ;  $P = 0.03$ ), WC (cm) ( $-5.57 \pm 5.64$  vs  $-2.32 \pm 5.95$ ;  $P = 0.01$ ) and WHR ( $-0.05 \pm 0.06$  vs  $-0.02 \pm 0.07$ ;  $P = 0.04$ ). Furthermore, a greater change was found in hs-CRP levels (mg/L) ( $-2.06 \pm 1.18$  vs  $-0.97 \pm 0.82$ ;  $P = 0.03$ ), prothrombin time (s) ( $1.41 \pm 2.34$  vs  $-0.41 \pm 2.17$ ;  $P < 0.001$ ), activated partial thromboplastin time (s) ( $0.26 \pm 3.70$  vs  $-1.78 \pm 3.56$ ;

$P = 0.04$ ) in modified alternate-day fasting diet when compared to calorie restriction diet. However, there was no difference in TNF- $\alpha$  or IL-6 and fibrinogen between groups ( $P > 0.05$ ). Conclusions: These findings suggest that a modified alternate-day fasting diet can be a beneficial alternative for the management of body weight, fat mass and WC as well as hs-CRP and coagulation factors levels among metabolic syndrome patients.

**Keywords:** Alternate-day fasting diet, energy restriction, inflammation, metabolic syndrome

## Introduction

Metabolic syndrome (MetS) is characterized by a cluster of interconnected biochemical, clinical, physiological and metabolic factors, leading to an increased risk of type 2 diabetes mellitus, cardiovascular disease, and all-cause mortality [1, 2]. Insulin resistance, elevated blood pressure, abdominal obesity, endothelial dysfunction, atherogenic dyslipidemia, chronic stress and genetic susceptibility are the most preponderant risk factors contributing to MetS [3]. Due to an inexorably rising prevalence, MetS is regarded an important worldwide health problem and represents a large burden on healthcare systems and resource utilization [2, 4]. It has been suggested that excess consumption of high-calorie food and having a sedentary lifestyle are the most common cause of developing, and indeed progression, of MetS [5]. Several empirical studies have shown that obesity is connected with an increased production of inflammatory cytokines, which can facilitate the progression of insulin resistance [6–8]. In addition, there is an association between obesity and high levels of various coagulation factors, such as coagulation factor X (fibrinogen) levels, which is a common risk factor for stroke or Coronary Heart Disease (CHD) [9]. Thus, a reduction in energy intake might, conceivably, have a key role in the treatment of MetS, and, consequently, in reducing the risk of cardiovascular disease via mitigation of inflammatory index and coagulation factors in over-weight and obese populations [10].

A daily calorie restriction (CR) diet has been used as common strategy for weight loss; where such regimens require decreasing energy intake by 15 to 40% of baseline needs every day, whilst retaining sufficient nutrient intake [10]. Although CR is efficacious for weight loss in obese individuals, many people recognize it difficult to adhere to these diets [11]. Another dietary strategy, that may be more feasible in practice than daily CR, is an alternate day fasting (ADF) regimen, which consists of a “fast day”, where intake is limited to 25% of the individual’s energy needs, (approximately 500 calories) alternating with a “feed day”, where food is consumed ad-libitum (ad libitum food consumption) [12]. The positive effect of ADF diet on weight and visceral fat mass loss

among overweight adults have previously been demonstrated [13]. However, there is currently insufficient information in this strategy among MetS patients. As urbanization advances, concomitant to high-calorie food consumption and sedentary lifestyle induced obesity, presenting a more practical approach to prevent and/or control MetS remains as a critical challenge faced by healthcare systems, globally. Therefore, the present study was conducted to investigate the impact of ADF versus CR diet on inflammatory index and coagulation factors in patients with MetS. calculated using the formula suggested for randomized clinical based on type one error ( $\alpha$ ) = 0.05 and power = 0.80%. Considering 20% drop-out, the final sample size was 40 participants per group.

## Study design

A total of 80 individuals with MetS were eligible and entered in to the two-week run in period. Firstly, written informed consent was obtained from all participants after explanation of the goal and nature of the trial. Then, all participants were stratified for BMI, age and sex, and were randomly assigned to ADF or CR group for 4 months. Randomization was performed using by random-generation software. The participants were instructed to complete a personal, socioeconomic information and medical/health history questionnaire accompanied by a well-trained staff member at the start of the study. All subjects were informed to maintain their regular physical activity habits through the time of investigation, and not to consume any supplements and/or medications which might affect related markers. Participants were also asked to complete a physical activity and 3-days dietary record (over two weekdays and one weekend day) to determine compliance with the study's dietary goals. In addition, the participant's adherence with the respective diets was monitored by phone interviews during the week.

## Method

### Study participants

The current study was a single-center, randomized clinical trial. The experimental protocol was approved by the research ethics committee of the Isfahan University of Medical Sciences, Isfahan – Iran (IR.MUI.REC.1394.3.892). The study was performed in accord with the CONSORT statement recommendation [14]. Patients were identified and recruited from Sediqe-Tahere Heart Center between December 2015 and May 2016. MetS was diagnosed according to The Revised National Cholesterol Education Program Third Adult Treatment Panel (RNCEP: ATPIII) definition [15]. The key criteria for inclusion were patients with MetS confirmed by a specialist, age 25–60 years, and 25 body mass index (BMI)  $40 \text{ kg/m}^2$ . Subjects were excluded from the study if they had weight changes 5% for 3 months prior to the study, history of cardiovascular, renal, liver and metabolic disease, smoking or taking any medication in last 6 months which is known to impact on weight loss, inflammatory status and coagulation factors, following especial diet, breast feeding, post-menopausal or pregnant women. Sample size was

## Diet protocol

All patients were instructed to adhere to a personally prescribed diet. During the 4 months ADF period, subjects consumed a very low-calorie diet (75% energy restriction) during the 3 fast days (Saturday, Monday, Wednesday) and then consumed ad libitum without limitation on each feed day (4 days a week). ADF subjects were provided with meals on each fast day (ranging from 400–600 kcal), and consumed ad libitum at home on the feed day. The feed and fast days began at midnight each day, and all fast day meals were consumed between 12.00 pm and 2.00 pm to ensure that each subject was undergoing the same duration of fasting. Subjects were permitted to consume calorie-free foods such as water, tea, green tea, coffee without sugar (< 400 mg caffeine per day), non-starchy vegetable (such as lettuce, cucumber, green leaf, tomato) and sugar-free gums on a fast day and were encouraged to drink plenty of water. In the CR group, the baseline energy requirements for the subjects were assessed by Mifflin equation [16] and subjects consumed 75% energy needs each day. All subjects were required to prepare all of their meals at home, and were guided on how to make healthy food choices, by selecting low-fat meat and dairy options and increasing fruit and vegetable intake. Daily dietary carbohydrate, fat, and protein accounted for 52, 30 and 18% of ingested energy, respectively. The weekly schedule of dietary follow-up is presented as Table E1 in Electronic Supplementary Material 1.

## Blood sampling and biochemical analyses

A 10-milliliter fasting blood samples were drawn from each participant after a 12-h overnight fasting at pre and post-intervention to assess serum high sensitivity-C-Reactive Protein (Hs-CRP), Prothrombin time (PT), activated partial thromboplastin time (a-PTT), and fibrinogen. All serums were also separated by centrifugation and were stored at  $-70^{\circ}\text{C}$ . The serum hs-CRP concentration was assayed by using ELISA kits (LDN, Nordhorn, Germany). Serum concentrations of interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were determined by the enzyme linked immunoassay technique with available commercial kits (Pars Azmoon. Co., Tabriz, Iran). Fibrinogen was also measured using immunoturbidimetry tests (Pars Azmoon. Co., Tabriz, Iran) according to the manufacturer's instructions. The Duke method was applied to measure bleeding time while a fingertip was pricked via lancet to cause bleeding. All measures were conducted by a technician who was blind to the assigned treatment to each patient.

Body weight was measured by scale (Seca Hamburg Germany) to the nearest 0.1 kg in light clothing, standing unshod in the first visit and after each month for 4 months. Fat mass was evaluated via bioimpedance analyzer (BIA; BC-418, Tanita Europe, Amsterdam, NL) with participants standing on metal foot-plates while holding the handles. BMI was calculated using the standard formula [body mass (kg)/height ( $\text{m}^2$ )]. Waist circumference (WC) was evaluated at the level of the umbilicus and waist-to-hip ratio (WHR) was determined by divided WC on the hip measured at its greatest gluteal protuberance.

## Primary and secondary outcomes

The primary outcomes of the study were significant changes in body weight, BMI, fat mass, fat free mass, WC and WHR. The secondary outcome measurements included decreases in hs-CRP, TNF- $\alpha$ , IL-6, PT, a-PTT and Fibrinogen levels among participants.

## Statistical analysis

All statistical analyses were conducted by using Statistical Package for the Social Sciences (SPSS) software, version 21 (SPSS Inc, Chicago, IL, USA). Kolmogorov-Smirnov

and Levene's test was used to check for normality distribution of data and equality of variances, respectively. A paired t-test was used to detect the differences between post intervention measurements from baseline values. Differences in baseline characteristics measured between ADF and CR diet groups were detected with independent-sample t-tests or the Chi-square test with regard for the type of variables. Due to the comparison of changes between the 2 groups in primary and secondary outcomes, analysis of covariance (ANCOVA) test was applied while controlling for identified covariates. In addition, a repeated-measures ANCOVA was used for comparing the evolution of change in body weight, BMI, WC and WHR during the 4-months treatment among the 2 groups. Results are expressed as means  $\pm$  Standard Deviation (SD), and a P-value less than 0.05 was considered statistically significant.

## Results

As demonstrated in the study flow diagram (Figure 1), a total 80 patients were eligible and were randomly assigned into the ADF and CR groups.

During the follow-up phase, 2 patients from AFD [over 10% discontinued intervention ( $n = 2$ )] and 3 patients from CR group [over 10% discontinued intervention ( $n = 2$ ) and migration ( $n = 1$ )] were excluded. Finally, 75 subjects completed the trial and were included in the final analysis. The number of dropouts did not differ between the study groups ( $p > 0.05$ ).

There were no significant differences between groups in term of anthropometric measures, blood pressure and physical activity (Table 1).

Furthermore, the baseline dietary assessment based on 3-days dietary record was comparable in both groups (Table 2).

No adverse effects associated with following the diets were reported among participants in ADF or CR group throughout the trial.

## Primary outcomes

After 4-months intervention, a greater, significant, reduction in body weight (kg) ( $-6.43 \pm 4.34$  vs  $-4.11 \pm 4.27$ ;  $P = 0.02$ ), BMI ( $\text{kg/m}^2$ ) ( $-3.19 \pm 2.90$  vs  $-1.43 \pm 2.72$ ;  $P = 0.01$ ), fat mass (kg) ( $-5.88 \pm 3.84$  vs  $-3.72 \pm 3.03$ ;  $P = 0.007$ ), WC (cm) ( $-5.57 \pm 5.64$  vs  $-2.32 \pm 5.95$ ;  $P = 0.01$ ) and WHR ( $-0.05 \pm 0.06$  vs  $-0.02 \pm 0.07$ ;  $P = 0.04$ ) was observed in ADF group in comparison to CR. No significant difference was observed in change of fat free mass (kg) ( $-0.55 \pm 3.91$  vs  $-0.39 \pm 3.17$ ;  $P = 0.84$ ) between 2 groups (Figure 2 & Table 3).

Table 1. General characteristics of study participants.

Variables	ADF Diet group (N = 38)	CR group Diet (N = 37)	P-value
Age (year)	41.3 $\pm$ 8.65	43.1 $\pm$ 9.26	0.38
Sex (M/F)	21 M/14 F	20 M/14 F	0.91
Body weight (kg)	89.4 $\pm$ 7.72	87.1 $\pm$ 8.17	0.41
Fat mass (kg)	37.1 $\pm$ 9.25	34.2 $\pm$ 9.80	0.21
Height (cm)	169 $\pm$ 10	168 $\pm$ 12	0.78
BMI ( $\text{kg/m}^2$ )	31.3 $\pm$ 3.12	31.2 $\pm$ 3.95	0.85
Waist circumference	106 $\pm$ 9.71	104 $\pm$ 10.2	0.23
Systolic blood pressure (mm Hg)	134 $\pm$ 9	137 $\pm$ 10	0.33
Diastolic blood pressure (mm Hg)	86 $\pm$ 4	85 $\pm$ 5	0.35
Physical activity (MET-h/day) at baseline	32.8 $\pm$ 6.21	32.1 $\pm$ 5.37	0.61
Physical activity (MET-h/day) at end of trial	33.7 $\pm$ 5.81	34.9 $\pm$ 5.78	0.38

Values reported as mean  $\pm$  sd. P-value was obtained from Independent samples t-test.

Abbreviations: ADF: Alternate Day Fasting; CR: Calorie restriction; BMI: Body Mass Index, F: Female, M: Male.

## Secondary outcomes

Compared to the CR diet, following the ADF diet led to a

larger, significant, reduction in hs-CRP concentrations (mg/l) ( $-2.06 \pm 1.18$  vs  $-0.97 \pm 0.82$ ;  $P = 0.03$ ). However, we did not detect any significant change in either TNF- $\alpha$  (pg/ml) ( $-3.47 \pm 5.77$  vs  $-2.21 \pm 5.04$ ;  $P = 0.60$ ) or IL-6 (pg/ml) ( $-1.08 \pm 2.70$  vs  $-0.61 \pm 2.82$ ;  $P = 0.49$ ) between groups (Table 3).

Adherence to ADF diet resulted in a significant increase in PT (s) ( $1.41 \pm 2.34$  vs  $-0.41 \pm 2.17$ ;  $P < 0.001$ ) and a-PTT (s) ( $0.26 \pm 3.70$  vs  $-1.78 \pm 3.56$ ;  $P = 0.04$ ) time. Furthermore, a trend to significant reduction Fibrinogen levels (mg/dl) ( $-34.57 \pm 76.63$  vs  $32.28 \pm 94.39$ ;  $P = 0.08$ ) was observed after ADF diet intervention in compare with CR diet (Table 3).

Table 2. Macronutrient intake of study participants at baseline.

Variables	ADF Diet group (N = 35)	CR group Diet (N = 34)	P-value
Energy (kcal/day)	2456 $\pm$ 286	2391 $\pm$ 316	0.37
Carbohydrate (g/day)	376 $\pm$ 67	352 $\pm$ 56	0.10
Protein (g/day)	83.7 $\pm$ 12.3	87.3 $\pm$ 12.8	0.23
Fat (g/day)	71.5 $\pm$ 10.3	69.8 $\pm$ 11.2	0.51
MUFA (g/day)	21.7 $\pm$ 5.8	19.9 $\pm$ 6.7	0.23
PUFA (g/day)	18.4 $\pm$ 8.2	17.8 $\pm$ 7.3	0.74

Abbreviations: ADF: Alternate Day Fasting; CR: Calorie restriction; MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid.

Table 3. Fat mass and Biochemical indexes at baseline and after 4-months intervention in subjects with metabolic syndrome.

Variables	Group	Baseline	End-of-trial	Changes	P-value*	P-value**
Fat mass (kg)	ADF	37.1 $\pm$ 9.25	31.2 $\pm$ 6.15	5.88 $\pm$ 3.84	0.001	0.007
	CR	34.2 $\pm$ 9.80	30.5 $\pm$ 5.02	3.72 $\pm$ 3.03	0.04	
Fat free mass (kg)	ADF	52.3 $\pm$ 8.67	51.8 $\pm$ 7.12	0.55 $\pm$ 3.91	0.59	0.84
	CR	53.7 $\pm$ 9.03	53.3 $\pm$ 7.32	0.39 $\pm$ 3.17	0.41	
Hs-CRP (mg/l)	ADF	4.27 $\pm$ 1.95	2.21 $\pm$ 2.61	2.06 $\pm$ 1.18	<0.001	0.03
	CR	3.75 $\pm$ 1.25	2.78 $\pm$ 1.02	0.97 $\pm$ 0.82	0.001	
TNF- $\alpha$ (pg/ml)	ADF	18.6 $\pm$ 8.36	14.8 $\pm$ 6.22	3.47 $\pm$ 5.77	0.08	0.60
	CR	17.2 $\pm$ 7.38	16.4 $\pm$ 5.69	2.21 $\pm$ 5.04	0.09	
IL-6 (pg/ml)	ADF	8.73 $\pm$ 3.26	7.65 $\pm$ 2.52	1.08 $\pm$ 2.70	0.12	0.49
	CR	7.47 $\pm$ 2.10	6.86 $\pm$ 2.96	0.61 $\pm$ 2.82	0.38	
PT (s)	ADF	12.7 $\pm$ 1.67	14.1 $\pm$ 2.01	1.41 $\pm$ 2.34	0.01	<0.001
	CR	14.1 $\pm$ 1.36	13.7 $\pm$ 1.61	0.41 $\pm$ 2.17	0.35	
a-PTT (s)	ADF	33.4 $\pm$ 3.50	33.7 $\pm$ 3.91	0.26 $\pm$ 3.70	0.71	0.04
	CR	34.4 $\pm$ 2.90	32.6 $\pm$ 3.73	1.78 $\pm$ 3.56	0.01	
Fibrinogen (mg/dl)	ADF	264 $\pm$ 53.6	230 $\pm$ 69.1	34.6 $\pm$ 76.6	0.03	0.08
	CR	219 $\pm$ 94.5	251 $\pm$ 65.5	32.3 $\pm$ 94.3	0.10	

Vale reported as mean  $\pm$  sd. \*P-value was obtained from Paired t-test. \*\*P-value was obtained from ANCOVA test adjusted by age, sex and baseline BMI. Abbreviations: ADF: Alternate day fasting; CR: Calorie restriction; hs-CRP: high-Sensitivity C-reactive protein; IL-6: interleukin-6; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ ; PT: Prothrombin time, a-PTT: activated limited thromboplastin time.



## Discussion

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Present study demonstrated that following the ADF diet for 4 months among patients with MetS had a beneficial effect on body weight, BMI, fat mass, WC, WHR, hs-CRP, PT, a-PTT levels in comparison to a CR diet, but did not affect fat free mass, TNF- $\alpha$  and IL-6 levels. Also, a trend towards significant reduction in fibrinogen levels was observed after ADF diet intervention in comparison to the CR diet.

Obesity is regarded as one of the principal risk factors in the development and progression of MetS [17]. Our study revealed that although both diets (ADF and CR) can lead to weight loss, as well as decrements in WC and fat mass (but not in fat free mass) after 4 months; however, the effect of the ADF diet on weight loss was greater than the CR diet. These findings were in accordance with some previous studies. For instance, Johnson et al. [18] reported that ADF diet administration resulted in 4 kg weight loss after 4 weeks in overweight individuals with moderate asthma (18). Similar results were also reported in studies using an ADF diet intervention on healthy overweight and obese adults; where it was reported that longer ADF administration may result in greater weight loss, and the authors suggested that the ADF diet can be a viable dietary option to help obese individuals lose, and manage, weight [19, 20].

Energy balance plays a mitigating role in body weight management, and weight loss correlates with a reduction in the total energy intake [21, 22]. Although the primary reason for greater weight loss in the ADF group may be attributed to a difference in total energy intake per week, participants in ADF group reported that they experienced lower appetite than before the intervention. It is conceivable that a change in appetite regulating hormones may have influenced our results. In animal models, it was reported that treatment with ADF can increase adiponectin concentrations, whilst decreasing resistin and leptin [23, 24]. However, in this study, we did not assess appetite related hormones and this effect was only reported anecdotally by patients, necessitating further studies which specifically examine the effect of ADF on appetite.

Another notable benefit of ADF vs CR for weight loss is the comparative ease in adherence. In conventional CR regimens, food consumption must be limited every day [25, 26], however, ADF diet require energy restriction only every other day which enhances adherence to dietary restriction protocols [27]. Also, in our study, the participants reported that ADF was comfortable to follow for an extended period. As weight loss is directly related to degree of dietary adherence [28], the high compliance rate to the ADF regimen plays a pivotal role in the total weight loss achieved.

The findings of the present study indicated that following an ADF diet results in a greater reduction in fat mass and waist circumference when compared to CR. Although several studies have shown that CR can decrease visceral fat mass, this reduction is caused by decreasing overall body fat loss [29–31]. However, the ADF can elicit a pronounced visceral fat mass reduction, which makes it an efficacious option in the management of abdominal obesity. Previous studies have also reported results in accordance with our findings; for example, Varady et al., [23] showed that 4-weeks adherence to ADF can decrease visceral fat and redistribute fat to subcutaneous compartments. Bhutani et al., [32] reported a favorable effect of 8-weeks ADF on obesity treatment, where body weight, waist circumference and fat mass was markedly decreased. Moreover, Varady et al. [33] also showed that following an ADF diet resulted in a reduction of  $3.6 \pm 0.7$  kg of fat mass among normal and overweight subjects after 8 weeks. Because visceral fat mass and WC are strongly associated with insulin resistance, one of the main causes of MetS, ADF may be a promising alternative strategy for improvement and management of MetS.

Inflammation is a critical risk factor for several chronic diseases. In the present study, although a significant reduction in hs-CRP was observed after following ADF as compared to the CR diet, no significant change was found in TNF- $\alpha$  and IL-6 between groups. In contrast with present study, Moro et al. [34] showed that eight weeks of time-restricted feeding can reduce TNF- $\alpha$  and IL-6 compared to normal diet. In this study which was conducted on thirty-four resistance-trained males, the participants in time-restricted feeding group received 100% of their energy during 8 hours and fasted for remaining 16 hours of each day. This discrepancy between our results in these inflammatory factors and Moro et al. [34] study might be due to the difference between protocol of fasting diet. Unlike our study, the participants fasted every day in Moro et al. [34] study, therefore, it is reasonable that we expected more beneficial effect on metabolic markers such as inflammatory factors. On the other hand, the recruited subjects in Moro et al. [34] study was also different from us (resistance-trained male vs Met) which might be resulted from the difference between findings.

Animal studies [35–37] have previously reported that ADF can improve inflammation by suppressing gene expression of inflammatory factors including TNF- $\alpha$  and IL-1 $\beta$ . Further suggesting that ADF may reduce the expression of nuclear NF- $\kappa$ B proteins which modulates the transcription of pro-inflammatory cytokines, acute phase proteins and chemokines such as interleukins, serum amyloid A, CRP and TNF- $\alpha$  [38]. It is also suggested that intermittent fasting results in activation of stress-induced pathway and enhances the generation of special proteins, where their transcription is induced in stressful conditions, including heat shock protein (HSP) 70 [39]. HSP 70 generally increases in response to severe conditions such as energy depletion, protein degradation and oxidative stress [40, 41]. In addition to attach to unfolded or misfolded proteins to help refold protein and ensure normal configurations, HSP 70 exerts anti-inflammatory and anti-apoptosis activities [42]. In addition, a decrease in fat mass can facilitate a reduction in CRP levels [43], which seems to be the mechanism for CRP reduction in the ADF group in our study.



Fibrinogen is a putative inflammatory factor which is involved in acute phase reaction and tend to be higher in obese individuals than people with normal weight [44]. In the present study, the fibrinogen levels significantly decreased in ADF group and increased in CR group, however, this difference was not statistically significant between two groups. PT and a-PTT was increased in ADF group and decreased in CR group, and these changes were statistically different between two groups. Only limited information has been reported regarding the impact of dietary intervention on coagulation factors. Some studies have reported that reductions in fibrinogen are correlated with decreasing in fat mass [45]. Fibrinogen is an acute phase protein and its effect may change depending on the host factors [46]. It is possible that inflammatory mechanisms are involved in postprandial coagulation activation [47] ((Author: add to references list)). So, ADF and CR diets both may be able to influence postprandial coagulation activation. However, the result from various reports are inconsistent and a precise reason for changes in fibrinogen, PT and a-PTT remains unclear. Further studies are required to clarify the possible relationship between adherence to a weight loss inducing diet and coagulation factors.

To the best of our knowledge, the present study was the first to investigate the effect of an ADF vs CR diet on body weight, inflammation and coagulation factors. However, there are several limitations that should be considered. First, due to the nature of dietary intervention studies, we could not perform trial in blinded fashion. Second, the sample size and duration of intervention was relatively short. However, even in this short period, we could show the prominent beneficial effects of ADF on MetS. Third, the compliance with diet by participants was determined through self-reporting, which might have resulted in misstatements; however, in order to reduce this bias, we endeavored to monitor participants via phone interviews throughout intervention, and completion of a 3-day food record.

## Conclusion

Present study suggests that ADF is a more efficacious strategy in managing body weight, fat mass and waist circumference in individuals with MetS. In addition, we demonstrate that a benefit of ADF is the ability to elicit decreases in hs-CRP, and improvements in PT and a-PTT, compared to a CR diet. These findings provide better insight into the capability of ADF vs CR for weight loss and management. However, further work is needed to generalize the findings to other populations with different health conditions, especially in nutrient deficient, at-risk individuals. Moreover, future studies are needed to investigate the long-term effect of ADF on metabolism, nutrient absorption and on holistic health.

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